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Care of children and adolescents with gender dysphoria

Summary

Summary

The National Board of Health and Welfare (NBHW) has been commissioned by the Swedish government to update the national guidelines on care of children and adolescents with gender dysphoria, first published in 2015 [1]. Guidelines chapters are updated stepwise and this report contains revised guidance on psychosocial support and diagnostic assessment, and on puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment. This report thus replaces the corresponding chapters in the publication from 2015. Remaining chapters and the updated guidelines as a whole will be published later in 2022. In response to comments received during external review, two new chapters have been added, named *New recommendations on hormonal treatment – their reasons and consequences* and *Non-binary gender identity – current knowledge and a need for clarification*. Another difference compared to the guidelines from 2015 [1] is that the term “gender incongruence” is used alongside the term “gender dysphoria”. For explanations of terms and abbreviations, see Appendix 2. For a description of the scientific evidence and clinical experience underlying the recommendations and the work process, see Appendices 3 and 4.

The guidelines apply to children and adolescents, i.e. people under 18 years of age. In the medical text sections, the term children (barn) refers to persons who have not yet entered puberty, while the term adolescents (ungdomar) refers to people whose puberty has started. In the text sections relating to juridical regulations, only the term children (barn) is used and denotes people younger than 18 years of age. Finally, the term “young people” (unga) is sometimes used in text sections addressing both children and adolescents.

Introductory comment

The summary that follows and the introductory chapter describe that the updated recommendations for puberty suppression with GnRH-analogues and gender-affirming hormonal treatment have become more restrictive compared to 2015, and the reasons that they have changed. The new recommendations entail that a larger

proportion than before, among adolescents with gender incongruence referred for diagnostic assessment of gender dysphoria, will need to be offered other care than hormonal treatments. Questions on how to ensure that all young people suffering from gender dysphoria be taken seriously and confirmed in their gender identity, well received and offered adequate care are becoming increasingly relevant, and will need to be answered during the ongoing restructuring of certain care for gender dysphoria into three national specialised medical care services (NBHW decision in December 2020). The care for children, adolescents and adults with gender dysphoria in these three national specialised units aims to improve equality in care, coordination and dialogue, and may enhance the implementation of national guidelines.

Recommendations and criteria for hormonal treatment

For adolescents with gender incongruence, the NBHW deems that the risks of puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment currently outweigh the possible benefits, and that the treatments should be offered only in exceptional cases. This judgement is based mainly on three factors: the continued lack of reliable scientific evidence concerning the efficacy and the safety of both treatments [2], the new knowledge that detransition occurs among young adults [3], and the uncertainty that follows from the yet unexplained increase in the number of care seekers, an increase particularly large among adolescents registered as females at birth [4].

A systematic review published in 2022 by the Swedish Agency for Health Technology Assessment and Assessment of Social Services [2] shows that the state of knowledge largely remains unchanged compared to 2015. High quality trials such as RCTs are still lacking and the evidence on treatment efficacy and safety is still insufficient and inconclusive for all reported outcomes. Further, it is not possible to determine how common it is for adolescents who undergo gender-affirming treatment to later change their perception of their gender identity or interrupt an ongoing treatment. An important difference compared to 2015 however, is that the occurrence of

detransition among young adults is now documented [3], meaning that the uncertain evidence that indicates a low prevalence of treatment interruptions or any aspects of regret is no longer unchallenged. Although the prevalence of detransition is still unknown, the knowledge that it occurs and that genderconfirming treatment thus may lead to a deteriorating of health and quality of life (i.e. harm), is important for the overall judgement and recommendation.

To minimize the risk that a young person with gender incongruence later will regret a gender-affirming treatment, the NBHW deems that the criteria for offering GnRH-analogue and gender-affirming hormones should link more closely to those used in the Dutch protocol, where the duration of gender incongruence over time is emphasized [5-7]. Accordingly, an early (childhood) onset of gender incongruence, persistence of gender incongruence until puberty and a marked psychological strain in response to pubertal development is among the recommended criteria. The publications that describe these criteria and the treatment outcomes when given in accordance [5, 6, 8] constitute the best available knowledge and should be used as guidance.

To ensure that new knowledge is gathered, the NBHW further deems that treatment with GnRH-analogues and sex hormones for young people should be provided within a research context, which does not necessarily imply the use of randomized controlled trials (RCTs). As in other healthcare areas where it is difficult to conduct RCTs while retaining sufficient internal validity, it is also important that other prospective study designs are considered for ethical review and that register studies are made possible. Until a research study is in place, the NBHW deems that treatment with GnRH-analogues and sex hormones may be given in exceptional cases, in accordance with the updated recommendations and criteria described in the guidelines. The complex multidisciplinary assessments will eventually be carried out in the three national units that are granted permission to provide highly specialized care services.

In accordance with the DSM-5, the recommendations in the guidelines from 2015 applied to young people with gender dysphoria in general, i.e. also young people with a non-binary gender identity. Another criterion within the Dutch protocol is that the child has had a binary ("cross-gender") gender identity since childhood [5, 6].

It has emerged during the review process, that the clinical experience and documentation of puberty-suppressing and hormonal treatment for young people with non-binary gender identity is lacking, and also that it is limited for adults. The NBHW still considers that gender dysphoria rather than gender identity should determine access to care and treatment. An urgent work thus remains, to clarify criteria under which adolescents with non-binary gender identity may be offered puberty-suppressing and gender-affirming hormonal treatment within a research framework.

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Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria

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Abstract

Gonadotropin-releasing hormone analogues (GnRHa) are recommended as initial treatment for adolescents diagnosed with gender dysphoria, providing time to follow gender identity development and consider further treatment wishes without distress caused by unwanted pubertal changes. This has been described as an extended diagnostic phase. However, there are also concerns about the physical, neurocognitive, and psychosocial effects of this treatment. In this retrospective study, we document trajectories after the initiation of GnRHa and explore reasons for extended use and discontinuation of GnRHa. Treatment was considered appropriate in 143 (67%) of the 214 adolescents eligible for GnRHa treatment by virtue of their age/pubertal status, and all started GnRHa (38 transgirls, 105 transboys; median age, 15.0 years [range, 11.1–18.6] and 16.1 years [range, 10.1–17.9]). After a median duration of 0.8 years (0.3–3.8) on GnRHa, 125 (87%) started gender-affirming hormones (GAH). Nine (6%) discontinued GnRHa, five of whom no longer wished gender-affirming treatment. Thirteen had used GnRHa for longer than required by protocol for reasons other than logistics and regularly met with a mental health professional during this time, supporting the use of GnRHa treatment as an extended diagnostic phase. In conclusion, the vast majority who started GnRHa proceeded to GAH, possibly due to eligibility criteria that select those highly likely to pursue further gender-affirming treatment. Due to the observational character of the study, it is not possible to say if GnRHa treatment itself influenced the outcome. Few individuals discontinued GnRHa, and only 3.5% no longer wished gender-affirming treatment.

Keywords Gender dysphoria · Transgender · Gonadotropin-releasing hormone analogues · Hormone treatment · Gender identity

Introduction

Increasing numbers of young people diagnosed with gender dysphoria are seen by pediatric endocrinologists. Gender dysphoria is the persistent feeling of incongruence between gender identity (sense of being a man, woman, or other) and

the sex assigned at birth. The diagnosis gender dysphoria can be made if the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria are met (American Psychiatric Association, 2013). The prevalence of gender dysphoria among Dutch adolescents aged 12–18 years was recently estimated to be 1 in 6300 based on numbers of adolescents seeking medical treatment, with a ratio of transboys (assigned female at birth) to transgirls (assigned male at birth) of 1.9:1 (Wiepjes et al., 2018). Genetic, hormonal, psychological, and social factors may play a role, but the exact etiology of gender dysphoria remains unknown (de Vries & Cohen-Kettenis, 2012; Hembree et al., 2017; Martinerie et al., 2018).

Gender dysphoria in prepubertal children can be expressed by dislike of their physical sex characteristics and gender incongruent behavior. In many children, gender dysphoria will not persist, but if the gender dysphoric feelings intensify during puberty, they are thought to be unlikely to subside (de Vries & Cohen-Kettenis, 2012; Hembree et al., 2017; Zucker et al., 2011). When puberty starts (Tanner genital/breast stage

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2) and gender dysphoria persists, adolescents are eligible to start with puberty suppression using gonadotropin-releasing hormone analogues (GnRHa) (Coleman et al., 2011; Hembree et al., 2017). GnRHa treatment aims to give the adolescent the opportunity to explore their gender identity and time to consider if they wish to pursue gender-affirming treatment while development of unwanted secondary sex characteristics is suppressed in order to reduce distress (Hembree et al., 2017; Zucker et al., 2011). Effects of GnRHa on pubertal development are reversible. This is in contrast to gender-affirming hormones which have largely irreversible effects on secondary sex characteristics and may compromise fertility after prolonged use (De Roo, Tilleman, T'Sjoen, & De Sutter, 2016; Hembree et al., 2017).

Short-term adverse effects of GnRHa are hot flushes at the start of the treatment and sometimes mood alterations and fatigue (Delemarre-van de Waal & Cohen-Kettenis, 2006; Hembree et al., 2017; Schagen, Cohen-Kettenis, Delemarre-van de Waal, & Hannema, 2016). Few data are available on long-term adverse effects. Bone mineral density may be affected (Klink, Caris, Heijboer, van, & Rotteveel, 2015; Vlot et al., 2017), and since puberty is an important period for brain development (Sisk & Zehr, 2005), puberty suppression with GnRHa might also influence brain development. There is a lack of studies investigating effects of GnRHa on the brain. One study examined executive function and concluded that GnRHa treatment had no detrimental effects on performance (Staphorsius et al., 2015). However, a longitudinal study among 25 adopted girls treated with GnRHa for early puberty reported a decrease in IQ from 100.2 ± 12.7 to 93.1 ± 10.5 with a significant decline of performance score during treatment, but it was concluded that the decrease in IQ was not clinically relevant (Mul et al., 2001). A limitation of the study was the lack of a control group. A second small cross-sectional study of girls treated with GnRHa because of precocious puberty found no significant difference in cognitive functioning, behavioral, and social problems compared to healthy age-matched controls, but the study did not have enough power to detect differences smaller than one standard deviation (Wojniesz et al., 2016). Wojniesz et al. did report that emotional reactivity was possibly higher in girls treated with GnRHa although these results were not conclusive. Girls with early or precocious puberty are treated at a younger age so it is unclear to what extent these results apply to adolescents treated with GnRHa for gender dysphoria. Further studies are needed to assess if and what effects GnRHa have on various aspects of brain development in adolescence.

Opinions about the use of GnRHa vary (Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & de Vries, 2015). Arguments for the use of GnRHa that have been brought forward are the benefit of early treatment with GnRHa for mental health and quality of life (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011). Furthermore, it gives the adolescent

and treatment team more time to explore the adolescent's gender identity and treatment wishes (Hembree et al., 2017). If the adolescent pursues gender-affirming treatment, some surgeries may not be necessary or less invasive as secondary sex characteristics are less developed. Early treatment is correlated with better postsurgical outcomes, possibly because of a physical appearance more in line with the affirmed gender (Cohen-Kettenis & van Goozen, 1997; Leibowitz & de Vries, 2016). However, this may not be of equal importance to all adolescents and early puberty suppression also precludes certain surgeries such as penile inversion vaginoplasty by limiting penile growth. Some have argued that puberty-blocking treatment prevents devastating psychological and physical harms including suicide and that adolescents should therefore be able to access this treatment even without parental approval (Dembroff, 2019; Priest, 2019), but others have underscored that there is no evidence that puberty suppression prevents suicide and that the risk of suicide, although high, should not be overstated and should be seen in comparison with a clinical comparison group rather than the general population (Antommara, Shapiro, & Conard, 2019; Baker, 2019; Zucker, 2019).

Arguments against the use of GnRHa that have been raised include possible long-term adverse effects on health, psychological, and sexual functioning (Laidlaw, Cretella, & Donovan, 2019; Richards, Maxwell, & McCune, 2019; Vrouenraets et al., 2015). Some state that adolescents may be unable to make far-reaching decisions at a young age, especially in the presence of comorbid psychiatric conditions, which are common among youth with gender dysphoria (Korte et al., 2008; Laidlaw et al., 2019; Vrouenraets et al., 2015). Furthermore, gender identity develops and may change during adolescence. Concerns have been raised that the use of GnRHa may influence this process and might increase the likelihood of persistence of gender dysphoria (Korte et al., 2008; Laidlaw et al., 2019; Richards et al., 2019; Stein, 2012; Vrouenraets et al., 2015). It is unknown if the use of GnRHa prevents resolution of gender dysphoria (Korte et al., 2008). Many prepubertal children with gender dysphoria no longer experience gender dysphoria in adolescence, and the experience of romantic and sexual attraction is thought to play an important role in this process (Steensma, Biemond, de Boer, & Cohen-Kettenis, 2011). Some may come to understand themselves as homosexual or bisexual (Steensma et al., 2011). GnRHa, by blocking sexual development, might interfere with this process (Korte et al., 2008). Another concern is that although GnRHa treatment is to be used as an extended diagnostic phase, the start of it may lead the adolescents and parents to assume that transgender outcome is the only possible outcome which may prevent exploration of other possibilities (Leibowitz & de Vries, 2016).

To gain more insight into the use of GnRHa in adolescents with gender dysphoria, the current study aims to document trajectories after the initiation of GnRHa, i.e., discontinuation

of GnRHa, prolonged use of GnRHa, and initiation of gender-affirming hormones; to investigate the duration of GnRHa treatment; and to explore reasons for extended use and discontinuation of GnRHa.

Method

Participants

This is a single-center retrospective study. Out of 269 children and adolescents registered at the Curium-Leiden University Medical Centre gender clinic in Leiden, the Netherlands, 214 were pubertal and within the appropriate age range for treatment at our pediatric clinic. Out of these, 143 (67%) had started GnRHa treatment between November 2010 (when the clinic first started) and January 1, 2018. The study population consisted of these 143 adolescents (38 transgirls, 105 transboys). Not included in the study were children and adolescents in whom gender dysphoria was not diagnosed ($n = 39$), those who had coexisting problems that interfered with the diagnostic process and/or might interfere with successful treatment ($n = 9$), those that did not wish hormonal treatment ($n = 4$), those in whom the diagnostic evaluation was still ongoing ($n = 10$), and those who had stopped to attend appointments ($n = 9$).

Of adolescents who had started GnRHa, treatment status as of 1 July 2019 was reviewed. If they had used GnRHa monotherapy for more than 3 months longer than minimally required before the start of gender-affirming hormones according to the local protocol (see below for description of the treatment protocol), the reason for this was noted. The 3 months was chosen to select those who may have had a prolonged diagnostic phase rather than those in whom gender-affirming hormone therapy started slightly later due to logistical issues such as rescheduling of an appointment. Adolescents who had started GnRHa treatment and had stopped this treatment were included in a detailed review. Baseline characteristics such as age and gender and data on the start, duration, and discontinuation of treatment were recorded from the medical files, as well as reasons given for the discontinuation of GnRHa treatment and the adolescents' and parents' views on the treatment.

Procedure

Before the start of GnRHa treatment, all adolescents had a diagnostic evaluation by a pediatric endocrinologist and mental health professional (MHP) to confirm the diagnosis of gender dysphoria according to the DSM-5 criteria (American Psychiatric Association, 2013), to assess the presence of any medical, psychiatric, or psychosocial problems that might interfere with treatment, to assess if the adolescent was able to give

informed consent for the treatment and to confirm that puberty had started, as recommended by current guidelines (Hembree et al., 2017). This evaluation usually consisted of approximately six visits (more if necessary) of the adolescent with an MHP in 6–12 months in addition to interviews with parents/guardians. All adolescents gave written informed consent for the treatment. Informed consent from parents/guardians was also required if the adolescent was < 16 years old. After the start of GnRHa treatment, follow-up visits were scheduled with the pediatric endocrinologist and MHP, usually every 3 months in the first year and every 3–6 months thereafter, to evaluate satisfaction with the treatment, adequacy of puberty suppression, and any side effects. In the case of mental health issues (psychiatric morbidity but also issues such as difficulty to express oneself and doubts about one's gender identity), adolescents were either seen more frequently by the psychologist of the gender team or referred to a local MHP for therapy.

According to the local protocol, adolescents were eligible for gender-affirming hormone treatment from the age of 16 years and after at least 6 months of GnRHa treatment. No maximum time of use of GnRHa was defined in the protocol. From 2016, adolescents who had already been treated with GnRHa for at least 3 years were eligible for gender-affirming hormone treatment from the age of 15 years. From 2017, those who had been treated with GnRHa for at least 2 years and were 15 years old were eligible. Before the start of gender-affirming hormones, evaluation by a MHP and pediatric endocrinologist took place to assess the indication, any contraindications, and ability to give informed consent for this treatment. If adolescents had discontinued GnRHa treatment, there was a follow-up appointment at which adolescents and parents were asked about current feelings regarding gender identity and how they looked back on the treatment.

Results

During the study period, 143 adolescents started GnRHa treatment (38 transgirls, 105 transboys). Median age at the start of treatment was 15.0 years (range, 11.1–18.6 years) in transgirls and 16.1 years (range, 10.1–17.9 years) in transboys. Of these adolescents, 125 (87%, 36 transgirls, 89 transboys) subsequently started treatment with gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRHa treatment (see Fig. 1). Median age at the start of gender-affirming hormones was 16.2 years (range, 14.5–18.6 years) in transgirls and 17.1 years (range, 14.9–18.8 years) in transboys. Five adolescents who used GnRHa had not started gender-affirming hormones at the time of data collection, because they were not yet eligible for this treatment due to their age. At the time of data collection, they had used GnRHa for a median duration of 2.1 years (1.6–2.8). Six adolescents had been referred to a gender clinic elsewhere for further treatment. One of these was

17 years old and eligible for gender-affirming hormones but initially indicated he needed more time to decide about testosterone treatment and subsequently stated that he wished to delay the start of this treatment until after his school examinations. The other five were not eligible yet due to their age at the time of referral. Nine had discontinued GnRHa treatment (see below), one of whom restarted GnRHa after 5 months. This individual and two others subsequently started gender-affirming hormone treatment (Fig. 1).

Prolonged Use of GnRHa

Twenty adolescents (3 transgirls and 17 transboys) had used GnRHa for longer than minimally required by protocol. One was the transboy mentioned above who needed more time to decide about testosterone treatment. He had used GnRHa for 2.5 years when he was referred from the pediatric clinic to a clinic for adults elsewhere. The other 19 adolescents had subsequently started gender-affirming hormones. The median duration of GnRHa monotherapy in these 19 adolescents was 1.0 year (0.8–2.4). Reasons for prolonged use of GnRHa were (sometimes there was more than one reason): unstable situation due to family issues such as lack of parental support and/or acceptance of gender dysphoria ($n=6$) or social problems such as lack of a safe home, excessive school absenteeism ($n=5$); (psychiatric) comorbidity ($n=8$) such as autism or depression; more time needed for decision about gender-affirming hormone treatment by the adolescent ($n=1$) or for further diagnostics by the gender team ($n=1$, because of non-binary aspects); and logistic issues such as missed/rescheduled appointments ($n=8$; in 7 this was the only reason). The 11 adolescents who received prolonged GnRHa treatment because of mental health and/or psychosocial problems had regular (approximately monthly on average) appointments with a psychologist at the gender clinic ($n=5$) and/or received support from a local MHP ($n=9$) during this period.

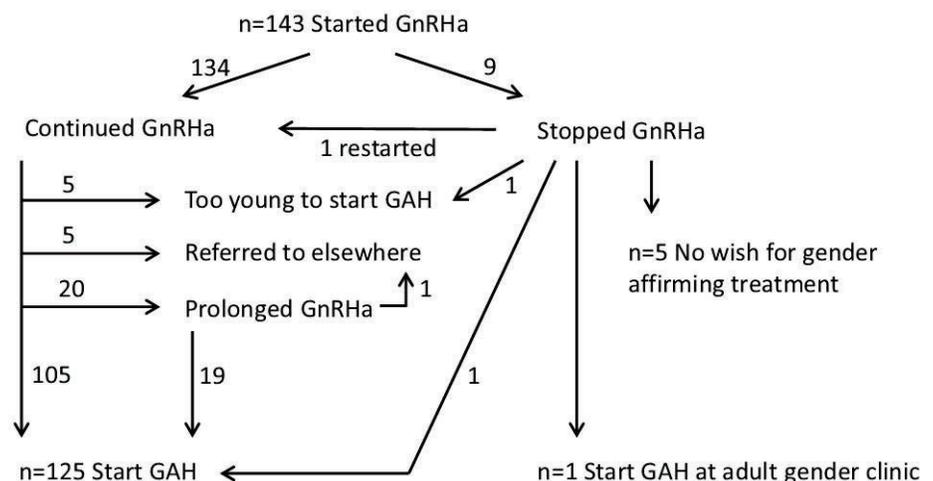
Discontinuation of GnRHa Treatment

From the 143 adolescents who started GnRHa treatment, nine (6%; one transgirl, eight transboys) stopped this treatment after a median duration of 0.8 years (0.1–3.0), at a median age of 15.0 years (13.4–18.9). Four individuals discontinued although they did wish further endocrine treatment because of gender dysphoria. One stopped treatment because of an increase in mood problems and suicidal thoughts and confusion attributed to GnRHa treatment and restarted treatment (gender-affirming hormone treatment) at an adult gender clinic elsewhere. He later indicated: “I was already fully matured when I started GnRHa, menstruations were already suppressed by contraceptives. For me, it had no added value” (transboy, age 19 years).

Another transboy experienced hot flushes, an increase in migraine, and had fear of injections in addition to stress due to problems at school and unrelated medical issues and therefore wished to temporarily discontinue GnRHa treatment after 4 months. He restarted 5 months later and subsequently started testosterone treatment. A third transboy experienced mood swings starting 4 months after he had begun GnRHa treatment. A year later, he started to frequently feel unwell and miss school. After 2.2 years, he developed severe nausea and rapid weight loss for which no cause was identified. Because of this deterioration of his general condition, he wished to discontinue GnRHa treatment after 2.4 years. He gradually recovered over the next 2 years. He subsequently started lynestrenol and testosterone treatment. The last adolescent had stopped GnRHa because his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections. He subsequently started lynestrenol to suppress menses; he is not eligible yet for testosterone treatment.

The five others (3.5%) no longer wished gender-affirming treatment. One adolescent had been very distressed about breast development at the start of GnRHa. She later thought

Fig. 1 Flow chart showing the trajectories of adolescents who started GnRH analogue (GnRHa) treatment. GAH gender-affirming hormone treatment



that she might want to live as a woman without breasts. She did not want to live as a boy and did not wish testosterone treatment and decided to discontinue GnRHa although she dreaded breast development and menstruation. Another adolescent had concurrent psychosocial problems interfering with the exploration of gender identity and did not currently wish treatment. When looking back on GnRHa treatment this individual said: “The decision to stop GnRHa to my mind was made by the gender team, because they did not think gender dysphoria was the right diagnosis. I do still feel like a man, but for me it is okay to be just me instead of a he or a she, so for now I do not want any further treatment” (adolescent assigned female sex at birth, age 16 years).

One adolescent felt more in between man and woman and therefore did not wish to continue treatment: “At the moment, I feel more like ‘I am’ instead of ‘I am a woman’ or ‘I am a man’” (adolescent assigned female sex at birth, age 16 years).

Another individual made a social transition while using GnRHa and shortly afterward decided to discontinue treatment. He indicated that he had fallen in love with a girl and had never had such feelings, which made him question his gender identity. At subsequent visits, he indicated that he was happy living as a man.

The last adolescent stated: “After using GnRHa for the first time, I could feel who I was without the female hormones, this gave me peace of mind to think about my future. It was an inner feeling that said I am a woman” (adolescent assigned female sex at birth, age 18 years).

The adolescents and parents were also asked about their views on GnRHa in the treatment protocol for gender dysphoria. All of them saw it as the first step in treatment, but it was also clear that it was used as an extended diagnostic phase. They all felt free to stop GnRHa. They had varying visions on the role of GnRHa in the treatment of gender dysphoria. Some stated it gave them time to think and feel who they were and what they wanted in the future and felt that without GnRHa treatment they would not have been able to make these decisions. Others stated that GnRHa should not be routinely offered before the start of gender-affirming hormones when adolescents are already fully matured, because of the lack of physical benefits. Instead, a consideration time of 6 months with psychological follow-up was suggested.

Discussion

The great majority of adolescents who started GnRHa subsequently started gender-affirming hormones as soon as they were eligible for this treatment. Very few discontinued treatment, although slightly more than in previous studies in which cohorts of transgender adolescents were described. Out of 333 adolescents that had started puberty suppression at the VUmc gender clinic in the Netherlands up until

December 2015, 1.9% stopped; reasons for discontinuation of GnRHa were not reported (Wiepjes et al., 2018). In the Canadian study by Khatchadourian, Amed, and Metzger (2014), one of 27 individuals who started GnRHa stopped the treatment due to emotional lability, not because the wish to pursue transition had subsided. In the current study, 6% of those who started GnRHa discontinued and 3.5% no longer wished gender-affirming treatment.

Several studies reviewed by Ristori and Steensma (2016) have found that much higher percentages (61–98%) of prepubertal children no longer experience gender dysphoria (“desist”) as adolescents. The period between 10 and 13 years seems to be a crucial period in which social changes (for example starting secondary school), the physical changes of puberty, and first romantic and sexual experiences may lead to either an increase or a decrease/resolution of gender dysphoria (Steensma et al., 2011). The adolescents that start GnRHa treatment have entered puberty and are mostly older than 13 years and may be past this critical period so that gender dysphoria may be more likely to persist. This may explain the lower percentage of resolution of gender dysphoria found in the studies of treated adolescents. In addition, the groups that started treatment in previous studies and in the current study consisted of selected adolescents that had had an extensive diagnostic process to establish if they met the eligibility criteria for treatment as well as the diagnostic criteria for gender dysphoria (Wiepjes et al., 2018). Alternatively, concerns have been raised that GnRHa treatment itself may increase the chances of persistence of gender dysphoria (Korte et al., 2008; Richards et al., 2019; Stein, 2012; Vrouenraets et al., 2015). Whether or not GnRHa treatment influenced gender identity development cannot be concluded from the current study due to its observational nature. The study does show that gender identity development was not suppressed in all, as a few adolescents discontinued GnRHa because they no longer experienced gender dysphoria, but it is unknown if gender dysphoria would have subsided in more adolescents in the absence of GnRHa treatment.

For one adolescent, the experience of falling in love made him doubt whether he was transgender. This is in line with previous findings that the first romantic experiences and the awareness of one’s sexual attraction play an important role in the resolution of gender dysphoria in adolescents (Steensma et al., 2011). This emphasizes the importance of this topic in the diagnostic evaluation. However, some adolescents may not have had any romantic or sexual experiences, especially if they present at an early age. In addition, transgender adolescents were shown to be less experienced, both sexually and romantically, compared to peers from the general population (Bunger, Steensma, Cohen-Kettenis, & de Vries, 2017). GnRHa treatment prevents the physical changes of puberty and is known to negatively affect sexual desire (Plosker & Brogden, 1994). Puberty suppression might thus decrease the chances of adolescents having romantic and sexual

experiences which might in turn influence gender identity development (Korte et al., 2008). This was not true for the adolescent in the current study who fell in love while using GnRHa and then decided to discontinue treatment, but it is uncertain if more adolescents would have had such experiences if they had not used GnRHa.

Two individuals who discontinued GnRHa indicated that they did not feel either male or female. A non-binary gender identity appears to be becoming more common among adolescents presenting at gender clinics (Butler, De Graaf, Wren, & Carmichael, 2018). For these adolescents, it may be more difficult to find out and understand their own gender identity and it is unclear what constitutes optimal care for this group.

Experienced side effects played a role in the decision to discontinue GnRHa treatment in three adolescents. However, for none of the adolescents who stopped GnRHa in the current study, were potential long-term side effects a reason to decline or discontinue GnRHa treatment. Lack of information about long-term effects of GnRHa use was not considered an important problem by interviewed adolescents with gender dysphoria in the study by Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, and de Vries (2016), but is seen as a major problem by many professionals (Vrouenraets et al., 2015).

In the current study, 13 adolescents who were eligible for gender-affirming hormone treatment used GnRHa monotherapy for longer than the minimum time required by protocol for reasons other than logistics. During this time, they received mental health support from a local MHP or from a psychologist from the gender team. This supports the idea that the time on GnRHa is used as an extended diagnostic phase where the adolescents can further explore their gender identity and treatment wishes and work on issues that might interfere with successful treatment. The great majority started gender-affirming hormones as soon as was possible within the treatment protocol, after a median duration of approximately one year. This does not mean that for them this time was not used as an extended diagnostic phase. Those who were youngest at the start of GnRHa were treated the longest, up to 3.8 years, with visits to the clinic every 3–6 months. In this period of growing up, becoming more independent, and discovering oneself, their development was followed by the team and discussed in relation to the treatment. Older adolescents, who presented after age 16 years, were often treated with GnRHa for the minimum period of 6 months. Generally, they were more mature than the younger adolescents at the start of the diagnostic process and many already had clear ideas about their treatment wishes. In adults, gender-affirming hormones are usually started directly after the diagnostic phase (Wiepjes et al., 2018).

The period of puberty suppression used in adolescents is considered worthwhile by some of the adolescents, as the individual in the current study who indicated it gave peace of mind to think about the future. On the other hand, some

postpubertal adolescents perceived little benefit of the treatment, as stated by one transboy who discontinued GnRHa in the current study. A possible benefit of GnRHa treatment for fully matured transgender boys may be the suppression of menstrual bleeding. Alternative methods may be used to achieve this, although GnRHa are more effective than progestins to immediately and fully suppress menstruation (Tack et al., 2016). Furthermore, many adolescents do not wish to use continuous oral contraceptives because of the fact that they contain “female” hormones and because of fear that breast size may increase. Adolescents should be counseled on all available treatment options and their (side) effects so that they can make an informed choice.

The relatively small size of the cohort that was described is a limitation of the current study as well as its retrospective character. The duration of follow-up was limited, and in some of the adolescents who stopped GnRHa treatment because they no longer experienced gender dysphoria, gender dysphoria might recur later in life. The observational design does not allow conclusions about any possible effect of GnRHa treatment on gender identity development. A randomized controlled trial in adolescents presenting with gender dysphoria, comparing groups with and without GnRHa treatment, could theoretically shed light on the effect of GnRHa treatment on gender identity development. However, many would consider a trial where the control group is withheld treatment unethical, as the treatment has been used since the nineties and outcome studies although limited have been positive (de Vries et al., 2014; Smith, van Goozen, & Cohen-Kettenis, 2001). In addition, it is likely that adolescents will not want to participate in such a trial if this means they will not receive treatment that is available at other centers. Mul et al. (2001) experienced this problem and were unable to include a control group in their study on GnRHa treatment in adopted girls with early puberty because all that were randomized to the control group refused further participation. An alternative approach that has been suggested to gain more insight into the effect of treatment on gender identity development is to collect baseline data at the time of referral from adolescents who are on a long waiting list for diagnostic evaluation and treatment and compare the percentage of these adolescents in whom gender dysphoria is still present after a certain period of time to that in adolescents on GnRHa treatment (Zucker, 2019).

In conclusion, this study shows that a small number of adolescents discontinued GnRHa treatment because they no longer wished gender-affirming treatment. This indicates that not all adolescents and parents assume that transgender outcome is the only possible outcome and shows that gender identity can still fluctuate when using GnRHa, at least in some adolescents. However, gender dysphoria subsided in a small number of adolescents and it is uncertain if this would have been different without GnRHa treatment. Some

adolescents used GnRHa for a prolonged period before starting gender-affirming hormones while regularly meeting with an MHP which is consistent with the use of GnRHa treatment as an extended diagnostic phase. The great majority who had started GnRHa treatment continued with gender-affirming hormones. It is important to take this into account when counseling adolescents who consider this treatment and their parents.

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Compliance with Ethical Standards

Conflict of interest MC de Vries and SE Hannema have received a lecture fee from Ferring. The other authors have nothing to declare.

Ethical Approval The study is part of an observational study on the effects of hormonal treatment in adolescents with gender dysphoria which was approved by the local medical ethical committee.

Informed Consent Adolescents who were included in the detailed review gave informed consent for the use of their data for this study, as well as their parents/guardians for adolescents younger than 16 years.

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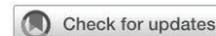
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TRANSGENDER HEALTH

The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets



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ABSTRACT

Background: Over the past decade, the number of people referred to gender identity clinics has rapidly increased. This raises several questions, especially concerning the frequency of performing gender-affirming treatments with irreversible effects and regret from such interventions.

Aim: To study the current prevalence of gender dysphoria, how frequently gender-affirming treatments are performed, and the number of people experiencing regret of this treatment.

Methods: The medical files of all people who attended our gender identity clinic from 1972 to 2015 were reviewed retrospectively.

Outcomes: The number of (and change in) people who applied for transgender health care, the percentage of people starting with gender-affirming hormonal treatment (HT), the estimated prevalence of transgender people receiving gender-affirming treatment, the percentage of people who underwent gonadectomy, and the percentage of people who regretted gonadectomy, specified separately for each year.

Results: 6,793 people (4,432 birth-assigned male, 2,361 birth-assigned female) visited our gender identity clinic from 1972 through 2015. The number of people assessed per year increased 20-fold from 34 in 1980 to 686 in 2015. The estimated prevalence in the Netherlands in 2015 was 1:3,800 for men (transwomen) and 1:5,200 for women (transmen). The percentage of people who started HT within 5 years after the 1st visit decreased over time, with almost 90% in 1980 to 65% in 2010. The percentage of people who underwent gonadectomy within 5 years after starting HT remained stable over time (74.7% of transwomen and 83.8% of transmen). Only 0.6% of transwomen and 0.3% of transmen who underwent gonadectomy were identified as experiencing regret.

Clinical Implications: Because the transgender population is growing, a larger availability of transgender health care is needed. Other health care providers should familiarize themselves with transgender health care, because HT can influence diseases and interact with medication. Because not all people apply for the classic treatment approach, special attention should be given to those who choose less common forms of treatment.

Strengths and Limitations: This study was performed in the largest Dutch gender identity clinic, which treats more than 95% of the transgender population in the Netherlands. Because of the retrospective design, some data could be missing.

Conclusion: The number of people with gender identity issues seeking professional help increased dramatically in recent decades. The percentage of people who regretted gonadectomy remained small and did not show a tendency to increase. **Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 2018;15:582–590.**

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Key Words: Transgender; Prevalence; Regret; Gender-Affirming Hormones; Gender-Affirming Surgery

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INTRODUCTION

Gender dysphoria (GD) refers to the distress related to a marked incongruence between one's assigned sex at birth and the experienced gender later in life.¹ In this study, we define transwomen as having a male birth assignment and transmen as having a female birth assignment who might receive medical treatment to adapt their physical characteristics to their experienced gender. This treatment can include puberty suppression (PS), gender-affirming hormonal treatment (HT), and gender-affirming surgery.

It has been widely observed that the transgender population is growing and broadening.^{2,3} This increase in the transgender population raises several questions, especially concerning the frequency of performing gender-affirming treatments with irreversible effects and regret from such interventions.

There are no reliable estimations of the current prevalence of transgender people who actually have received gender-affirming treatment (including HT), because most recent studies are based on questionnaires^{4,5} or data about gender-affirming surgery only.^{6,7} In most countries transgender care is performed by multiple health care providers (eg, university clinics or general practitioners), which makes it difficult to provide these numbers. In contrast, in the Netherlands, more than 95% of the transgender population has received treatment in only 1 center, the gender identity clinic at the VU University Medical Center (VUmc; Amsterdam, the Netherlands), currently known as the Center of Expertise on Gender Dysphoria.^{8–10} This center started treating adults in 1972. From 1987 to 2002, children and adolescents were seen by a mental health specialist in the Utrecht University Medical Center (Utrecht, the Netherlands). After they were considered eligible, they could receive medical treatment in the VUmc, which consisted of PS (usually by gonadotropin-releasing hormone analogues), followed by HT (see Kreukels and Cohen-Kettenis¹¹ for the treatment protocol for adolescents diagnosed with GD). After 2002, the Utrecht clinic stopped seeing adolescents and the diagnostics were performed in the VUmc. Adult people are referred to a psychologist or psychiatrist for the diagnostic phase after an initial screening. People diagnosed with GD can start HT if they are considered eligible. HT consists of testosterone for transmen and estrogens, often combined with antiandrogens, for transwomen. In the 1st year of HT, checkups are performed every 3 months. After a minimum of 12 months of HT, gender-affirming surgery can be performed, including mastectomy and hysterectomy with oophorectomy in transmen and breast augmentation and vaginoplasty (including orchiectomy) in transwomen. After gonadectomy (oophorectomy or orchiectomy), people are usually seen every 1 to 2 years for clinical follow-up.

In the present study we included the complete population seen at the gender identity clinic of the VUmc from 1972 through December 2015 to assess the current prevalence of transgender people who received medical treatment, the frequency of specific medical treatments performed, and the numbers of people who

received HT in line with their sex assigned at birth because they regretted undergoing gonadectomy.

METHODS

Study Design and Patient Selection

After approval of the local ethics committee, a retrospective medical record review was performed to identify all people seen in our gender identity clinic from 1972 until December 2015. Data were collected from the hospital registries of the VUmc. The total study population was defined as people who had been diagnosed with 1 of the following *International Classification of Diseases* diagnoses: 302.5 (transsexualism), 302.6 (gender identity disorder not otherwise specified), or 302.85 (gender identity disorder in adolescent or adult) according to the 9th edition or F64 (gender identity disorders) according to the 10th edition.¹² In addition, the administrative employees of our gender identity clinic registered everyone who was referred to our gender identity clinic since the early 1970s. People reported on this list also were included in the study population. Some people of this study population have been described in previous studies.^{9,13–18} People were excluded from the study if they had been registered at our gender identity clinic but had actually never visited the clinic or if they had presented with other complaints than gender identity issues. Because of the retrospective design and the large study population, necessity for informed consent was waived by our local ethics committee.

Hospital Registries

The hospital registries store clinical data obtained during regular patient care performed in our center, including medical diagnoses (since 1985), medication prescriptions (since 2000), surgical interventions (since 2006), laboratory test results (since 2004), radiology results (since 1993), and visit dates (since 2007). The 1st visit was defined as the 1st appointment with the psychologist, psychiatrist, pediatrician, endocrinologist, or gynecologist for health care related to gender identity.

Clinical Data Collection

Not all data were available from the hospital registries, particularly older data or surgeries performed in other centers. To generate the most reliable results, the medical records of all people who composed the study population were checked. All people were classified as transwomen or transmen (based on the sex assigned at birth), and date of birth and death were noted. The following categories were included: the individual was in the diagnostic stage, the individual did not start HT, or the individual was on HT. Start of HT was defined as the 1st date gender-affirming hormones were prescribed by a physician in our gender identity clinic after a confirmed GD diagnosis, irrespective of previous gender-affirming hormone use. Of the people who started HT, baseline and follow-up data, including

1st visit, medical history, medication use, prior gender-affirming hormone use, start date and type of PS and HT, and date of gonadectomy, were collected. Some people regretted the interventions they had undergone. Transwomen who started testosterone treatment after vaginoplasty or transmen who started estrogen treatment after oophorectomy and expressed regret were categorized as those who experienced regret. Reasons for regret as reported in their medical records were noted. Dates were set to the 1st of the month and personal identification data were removed from the research database.

Statistical Analysis

The total number of people visiting the clinic each year and their median age were reported separately for transwomen and transmen and were stratified for age at the 1st visit: children were younger than 12 years, adolescents were 12 to 18 years old, and adults were at least 18 years old. The percentage of people who started HT within 5 years after the 1st visit was reported for each year. The prevalence was calculated for people at least 12, at least 16, 12 to 18, 18 to 30, 30 to 50, and at least 50 years old by using the total number of people in these age groups who received medical treatment in our center until 2015, excluding deceased people. The total populations of these age groups in the Netherlands in 2015 were provided by the Central Bureau of Statistics of the Netherlands. The percentage of people who underwent gonadectomy within 5 years after starting HT was reported. For

calculation of the total percentage of the study population who had undergone gonadectomy, only people at least 18 years old who used HT for at least 1.5 years were included, because these were requirements for surgery. People who regretted their medical transition are reported as the percentage of the total population of transwomen and transmen who underwent gonadectomy. In adults, time from 1st visit to start of HT or gonadectomy, if applicable, are expressed as median days with interquartile range (IQR). Total follow-up time was calculated for every individual who started HT and was expressed as years from the 1st visit to the last visit. Prevalence with 95% CI was calculated using OpenEpi.¹⁹ All other analyses were performed using STATA 13.1 (StataCorp, College Station, TX, USA).

RESULTS

1st Visit

6,793 people presented for gender-affirming treatment, with more transwomen (65.2%) than transmen (34.8%; Table 1). The number of people attending the gender identity clinic increased over time (Table 2), whereas the median age of adults at the time of their 1st visit decreased (Figure 1). The median age at the 1st visit was younger for adult transmen (25 years; IQR = 21–35 years) than for adult transwomen (33 years; IQR = 25–42 years). Although historically more transwomen than transmen presented for treatment, more transmen than

Table 1. Treatment patterns of total study population, stratified for age groups and for transwomen and transmen*

	Transwomen	Transmen	Total	Ratio of transwomen to transmen
Total study population, N (%)	4,432 (65.2)	2,361 (34.8)	6,793 (100)	1.9:1
Adults (≥18 y)	3,809	1,624	5,433	2.3:1
Age (y) [†] , median (IQR; max)	33 (25–42; 81)	25 (21–35; 73)	31 (23–41; 81)	
Started HT [‡] , %	68.9	72.9	69.9	
Underwent gonadectomy , %	75.3	83.8	77.7	
Adolescents (12–18 y)	330	482	812	0.7:1
Age (y) [†] , median (IQR)	16 (15–17)	16 (15–17)	16 (15–17)	
Started PS [‡] , %	28.7	50.8	41.0	
Stopped PS, %	4.1	0.7	1.9	
Started HT [‡] without PS, %	33.9	30.8	32.2	
Underwent gonadectomy , %	79.5	77.2	78.2	
Children (<12 y)	293	255	548	1.1:1
Age (y) [†] , median (IQR)	8 (7–10)	9 (8–11)	9 (7–10)	
Started PS [‡] , %	33.6	49.1	40.3	
Regret [#] , % (n)	0.6 (11)	0.3 (3)	0.5 (14)	2.0:1

HT = gender-affirming hormonal therapy; IQR = interquartile range; max = maximum; PS = puberty suppression.

*From 1987 through 2002, children and adolescents were seen at the Utrecht University Medical Center and then at the VU University Medical Center only if they could begin medical treatment.

[†]Age is defined as the age at the 1st visit to the VU University Medical Center, Amsterdam.

[‡]Only those who reached the age of eligibility (usually ≥12 years old) could undergo PS.

[§]Only in people at least 16 years old.

^{||}Only people treated with gender-affirming hormones for at least 1.5 years and at least 18 years old (orchiectomy in transwomen and oophorectomy in transmen).

[¶]Those who were too old (≥18 years) after the diagnostic phase for PS could begin directly with HT.

[#]Only those people who underwent gonadectomy.

Table 2. Description of adult study population for every 5-year cohort

	1st visit, n	Started HT*, %	Age (y) at start of HT, median (IQR)	Previous HT, %	Underwent gonadectomy†, %
Transwomen (≥18 y)					
1972–1979	119	89.9	33 (26–40)	16.8	79.4
1980–1984	189	88.4	33 (25–40)	12.6	71.9
1985–1989	319	75.9	31 (25–39)	15.3	76.5
1990–1994	392	65.8	30 (25–41)	20.5	76.7
1995–1999	522	65.5	34 (27–41)	26.6	78.7
2000–2004	605	56.0	38 (30–45)	29.2	67.3
2005–2009	476	61.6	39 (29–47)	22.9	68.6
2010–2014	926 (138‡)	60.9‡	32 (23–42)‡	29.8‡	NA
Transmen (≥18 y)					
1972–1979	30	96.7	24 (21–30)	10.3	72.4
1980–1984	69	84.1	24 (21–32)	3.5	82.8
1985–1989	105	84.8	24 (21–30)	1.1	79.8
1990–1994	142	69.0	27 (21–33)	7.1	88.8
1995–1999	177	65.0	29 (24–37)	7.0	88.7
2000–2004	207	63.3	32 (26–39)	5.3	87.0
2005–2009	185	63.8	29 (23–37)	3.4	81.4
2010–2014	518 (70‡)	71.4‡	24 (21–37)‡	0‡	NA

HT = gender-affirming hormonal therapy; IQR = interquartile range; NA = not applicable.

*People who started HT within 5 years after the 1st visit.

†People who had this procedure within 5 years after the start of HT.

‡Only in people who had their 1st visit 5 years before December 31, 2015 (n = 138 transwomen; n = 70 transmen).

transwomen applied for treatment in 2015. This change in sex ratio was mainly due to the increase in adolescent transgender boys, because the ratio of transwomen to transmen in adults remained stable over time.

Prevalence and Treatment

At the end of 2015, 3,838 transgender people at least 16 years old had received medical treatment and were not deceased. Because the total population of people at least 16 years old in the Netherlands in 2015 was 13,870,426, the prevalence was 27.7 per 100,000 people (95% CI = 26.8–28.6), or 1:3,600. Stratification for transwomen and transmen showed a prevalence of 36.4 (95% CI = 35.0–37.8) per 100,000 people (or 1:2,800) for men (transwomen) and 19.3 (95% CI = 18.3–20.3) per 100,000 people (or 1:5,200) for women (transmen). The calculation of prevalence numbers of people at least 12 years old and specific age groups are presented in Table 3.

The percentage of adult people who started HT within 5 years after the 1st visit decreased over time, whereas the percentage of people who underwent gonadectomy within 5 years after starting HT remained stable (Figure 2). Of the total study population at least 18 years old treated with HT for at least 1.5 years, 75.6% of transwomen (n = 1,742) and 82.4% of transmen (n = 885) underwent gonadectomy. The median time from the 1st visit to the start of HT for adults was 327 days (IQR = 36–570 days) and from the 1st visit to gonadectomy was 1,029 days (IQR = 679–1,465 days). The median

follow-up time for people treated with HT was 6.4 years (range = 0.4–41.6 years).

Of adolescents, 41.0% started PS, whereas only 1.9% of these adolescents stopped PS and did not start HT (Table 1). 32.2% of adolescents started directly with HT, because they were too old (≥18 years) to start with PS after the diagnostic phase.

Regret

Regret was identified in 0.6% of transwomen and 0.3% of transmen who underwent gonadectomy. The characteristics of these people are presented in Table 4. Their ages at start of HT ranged from 25 to 54 years, and they expressed their regrets 46 to 271 months after initiation of HT. Reasons for regret were divided into social regret, true regret, or feeling non-binary. Transwomen who were classified as having social regret still identified as women, but reported reasons such as “ignored by surroundings” or “the loss of relatives is a large sacrifice” for returning to the male role. People who were classified as having true regret reported that they thought gender-affirming treatment would be a “solution” for, for example, homosexuality or personal acceptance, but, in retrospect, regretted the diagnosis and treatment.

DISCUSSION

The aim of this study was to generate a dataset of all individuals who presented to our clinic for gender-affirming care from 1972 to 2015. We found that the number of people with

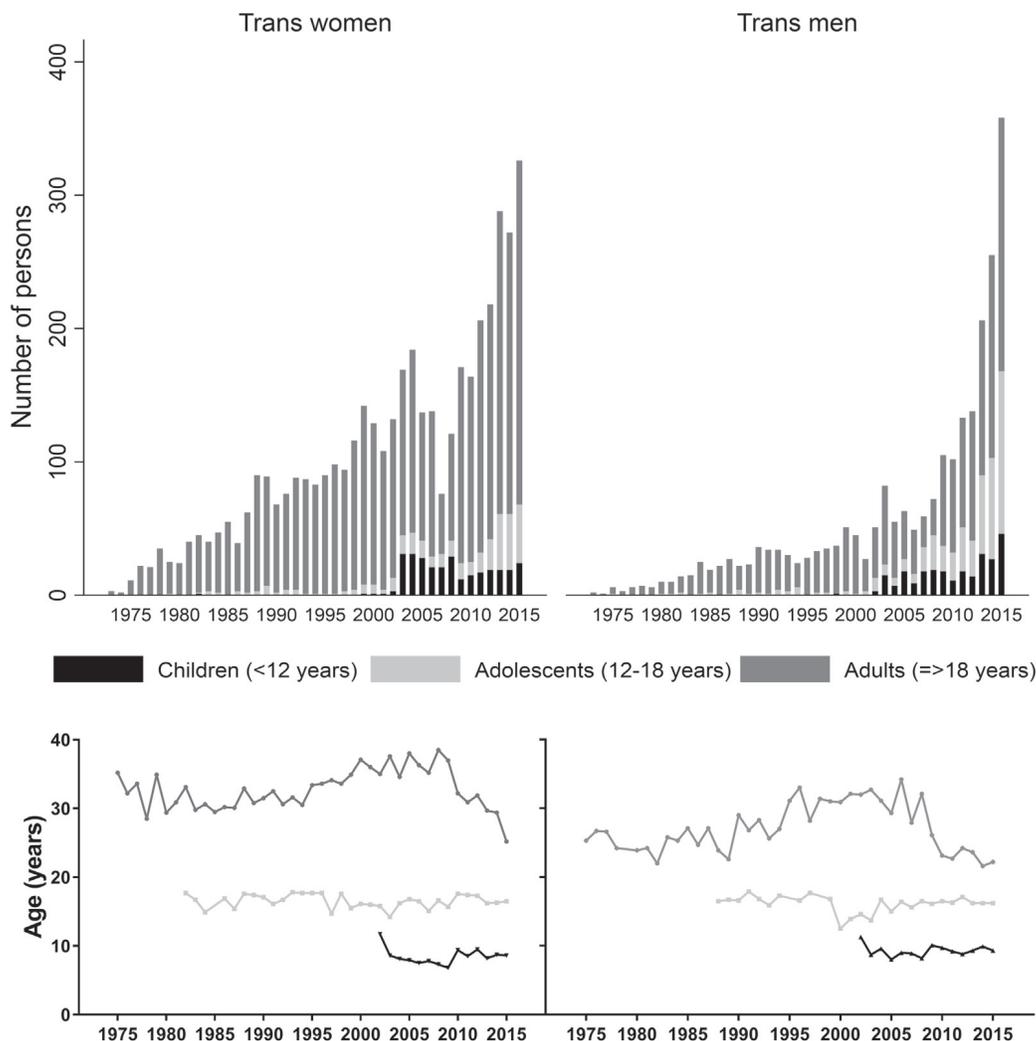


Figure 1. Number of people and median age for each year, stratified for transwomen and transmen and for children (<12 years), adolescents (12–18 years), and adults (≥18 years). Age is defined as age at the 1st visit to the VU University Medical Center, Amsterdam. From 1987 through 2002, children and adolescents were seen at the Utrecht University Medical Center and then at the VU University Medical Center only if they could begin medical treatment.

gender identity issues who sought professional help increased dramatically in recent decades and that the median age of adults at presentation decreased. The ratio of transwomen to transmen remained stable over the years for adults, whereas in adolescents

the population of transgender boys increased compared with the population of transgender girls. Currently, more transgender boys than transgender girls are seen. This phenomenon also has been described by Aitken et al.¹⁷ The age at the 1st visit was

Table 3. Prevalence numbers, specified for different age groups*

Age (y)	Total population		Male sex assigned at birth (transwomen)		Female sex assigned at birth (transmen)	
	Per 100,000	1 per	Per 100,000	1 per	Per 100,000	1 per
≥12	26.9 (26.1–27.8)	3,700	34.8 (33.5–36.2)	2,900	19.3 (18.3–20.3)	5,200
≥16	27.7 (26.8–28.6)	3,600	36.4 (35.0–37.8)	2,800	19.3 (18.3–20.3)	5,200
12–18	16.0 (13.9–18.4)	6,300	11.1 (8.8–14.1)	9,000	21.0 (17.7–25.1)	4,800
18–30	35.7 (33.5–38.2)	2,800	30.3 (27.4–33.4)	3,300	41.4 (37.9–45.1)	2,400
30–50	30.5 (29.0–32.2)	3,300	40.1 (37.6–42.8)	2,500	21.0 (19.2–23.0)	4,800
≥50	23.0 (21.9–24.2)	4,300	37.6 (35.5–39.8)	2,700	9.7 (8.7–10.8)	10,300

*Data are presented as number (95% CI).

Table 4. Characteristics of people with regret

Case	Type	Year started HT	Age (y) at start of HT	Year of gonadectomy	Time after HT (mo)	Time after gonadectomy (mo)	Reversal surgery	Reason for regret
1	M-F-M	1978	31	1979	±153	±130	None	Social acceptance
2	M-F-M	1982	25	1984	±54	±27	Mastectomy	Social acceptance
3	M-F-M	1986	47	1988	±216	±197	Mastectomy	Social acceptance
4	M-F-M	1988	33	1990	±186	±167	None	True regret
5	M-F-M	1988	38	1990	±70	±44	Mastectomy	Social acceptance
6	M-F-M	1991	41	1993	±67	±49	Mastectomy, vaginectomy, phalloplasty	Social acceptance
7	M-F-M	1991	38	1995	±271	±225	Mastectomy	True regret
8	M-F-M	1993	30	1994	±79	±61	None	Feels non-binary
9	M-F-M	1996	33	1997	±90	±73	Mastectomy, phalloplasty	True regret
10	M-F-M	1997	43	1999	±46	±27	Mastectomy	True regret
11	M-F-M	2004	54	2007	±130	±92	Mastectomy, vaginectomy	True regret
12	F-M-F	1987	25	1990	±91	±50	Breast augmentation, remove testicular implants	True regret
13	F-M-F	1990	34	1993	±102	±74	Remove testicular implants	Feels non-binary
14	F-M-F	1993	31	1997	±258	±212	None	True regret

F-M-F = female to male to female; HT = hormonal treatment; M-F-M = male to female to male.

older for adult transwomen than for transmen. The percentage of adult people starting HT within 5 years after the 1st visit decreased over time, whereas the percentage of people who underwent gonadectomy within 5 years after starting HT remained stable. Of the total population treated with HT, 77.8% underwent a gonadectomy. Only a very small percentage of people who underwent gonadectomy regretted their decision, expressed as the start of HT in line with their sex assigned at birth.

An explanation for the increase in referrals could be the increased attention in society and media, which contributes not only to awareness of the existence of GD and possibilities for medical treatment but also to greater social acceptance. In addition, information about transgender identities has become much more accessible through the internet within the past decade, which could lead to an earlier recognition of gender identity issues. Also, transgender and gender non-binary individuals might be more willing to access care and more access to care has become available.

The increase in the prevalence of people with GD who sought medical treatment in the Netherlands (1:11,900 transwomen and 1:30,400 transmen in 1990⁸ vs 1:2,800 transwomen and 1:5,200 transmen currently) suggests that the transgender population is dramatically increasing. The highest prevalence for transwomen was found for the 30- to 50-year age group (1:2,500), whereas that for transmen was found in the 18- to 30-year age group (1:2,400). Transgender people in the Netherlands seem to experience a reasonable degree of acceptance owing to a tolerant social climate in contrast to many other countries.²⁰ For example, medical costs are reimbursed by medical insurance companies, and it is possible to change the legal sex status (even without gonadectomy). These points can lead to a lower threshold to seek help, making this study population useful for an adequate estimation of the current prevalence of people with GD who seek medical treatment. More than 95% of transgender people are treated in our gender identity clinic. However, not all transgender people seek medical help. Some use self-medication or go abroad for treatment. Therefore, these numbers might still be an underestimation of the real prevalence. Our data represent a population that actively sought help in a medical setting. In 2012, a Dutch study of non-clinical people reported that 0.6% (1:167) of those with male sex assigned at birth and 0.2% (1:500) of those with female sex assigned at birth reported an incongruent gender identity with a wish for hormones or surgery.²¹ However, that was a population-based study with a response rate of 20.9%, which could lead to non-response bias. In addition, the existence of incongruent gender identities was based on self-report and no detailed assessment of GD was performed, which could have led to higher prevalence rates.

An interesting finding is the percentage of children who were referred in childhood (before 12 years of age) and who started PS when the GD persisted and the eligibility criteria were fulfilled. This 40% of children who started PS is almost identical to the 39% of persistence of childhood GD reported in a previous

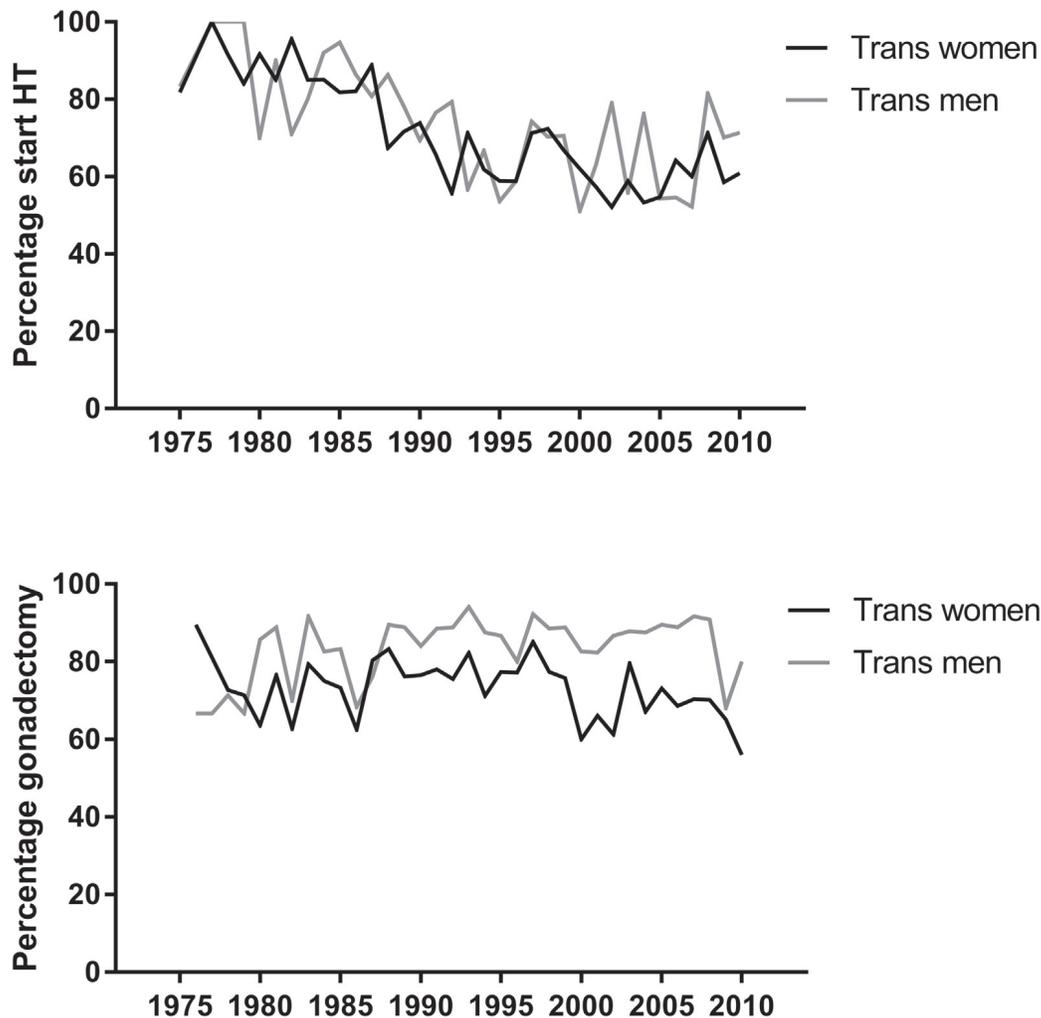


Figure 2. Top panel shows percentage of transgender adults beginning gender-affirming HT within 5 years after the 1st visit, stratified for transwomen and transmen. Bottom panel shows percentage of transgender adults with occurrence of gonadectomy within 5 years after starting HT for each year, stratified for transwomen and transmen. Year is defined as the year of the 1st visit. HT = gender-affirming hormonal treatment.

Dutch study (using a smaller cohort of children).²² In addition, the finding that the persistence is higher in natal girls (49.1%) compared with natal boys (33.6%) is in line with observations in previous follow-up studies on the persistence of GD in children (for an overview, see Ristori and Steensma²³).

Remarkably, we found a decrease over time in the percentage of referred adult people who actually started HT. This finding might be explained by the fact that in the past it was harder to find information about GD and its treatment, and only people with extreme types of GD managed to visit our gender identity clinic for treatment. Currently, owing to media attention and the internet, it is easier to access information about our gender identity clinic, making the threshold lower to search for help. This could have led to referrals of people with milder forms of GD and people who were not sure of their feelings and just wanted to explore these with a psychologist. Such people eventually might not pursue HT. Another explanation might be that not all transgender people want to undergo HT, such as transmen or people with a non-binary identity who only want a mastectomy.²⁴

By contrast, we noticed that the percentage of people who underwent gonadectomy within 5 years after the start of HT remained stable over time. At the start of the clinic in 1972, knowledge about transgender care was limited and only people who wished for a classic treatment, consisting of a diagnostic phase, HT plus social transitioning, and surgery (in this order), were treated. There was no room for partial treatments. Since the publication of the Standards of Care Version 6 in 2001, other types of treatment are offered.²⁵ In addition, in 2014, a change in Dutch law allowed transgender people without a wish to undergo gonadectomy to alter the sex on their birth certificate with a statement of an expert who declared that the individual was diagnosed with GD (Dutch civil law, article 1:28). Although these changes in clinical guidelines and the law might have led to a decrease in the number of transgender people choosing gonadectomy, the current results do not show this. However, the follow-up time of this study might be too short to notice such changes.

In the HT group, 22% of people who were eligible for surgery had not undergone gonadectomy. These numbers are

comparable with a study from Sweden²⁶ but larger than in a study from Belgium,²⁷ in which approximately 15% of transwomen and transmen did not undergo gonadectomy. A possible wish to carry a child could change these numbers in the future, because fertility has become a more important issue.

Despite the large increase in treated transgender people, the percentage of people who underwent gonadectomy but regretted their decision was still very small (0.5%). In a review by Pfäflin²⁸ in 1992, regret was reported by less than 1% of transmen and 1% to 1.5% by transwomen after gonadectomy. More recent studies have reported regret percentages of 0%^{29,30} to 2%⁷ and 6%³¹ after gonadectomy. 13 of the 14 people who regretted gonadectomy had started HT from 1978 through 1997 and 1 started in 2004. At best, this indicates that the diagnostic and eligibility criteria for treatment have improved over the past decade. Another explanation might be the altered treatment protocol, which also allowed people to receive HT without gonadectomy. Our findings could be an underestimation of people with regret after gonadectomy, because some might choose to go elsewhere for reversal therapy or might experience regret without pursuing reversal surgery or HT. Regret might not always result in a desire for reversal therapy, as it may be hidden from others. In addition, in our population the average time to regret was 130 months, so it might be too early to examine regret rates in people who started with HT in the past 10 years.

The Center of Expertise on Gender Dysphoria of the VUmc Amsterdam is the largest gender identity clinic in the Netherlands, where people of all ages, including children and adolescents, are treated. Life-time follow-up is recommended, making it a useful study population for collection of epidemiologic data and future long-term studies of treatment effects. However, there are some limitations. Because this is a retrospective chart review study, some data could be lacking. (i) Some people who once visited our clinic might not be reported in our database. However, we used several search strategies to identify the total study population, thereby decreasing the possibility of missing people. (ii) A large number of transgender people who had initially received treatment in our center were lost to follow-up. Although transgender people receive lifelong care, a large group (36%) did not return to our clinic after several years of treatment. Therefore, we could have missed some information on, for example, gonadectomies performed at other centers or people with regret.

CONCLUSIONS

We found that the prevalence of treated transgender people increased exponentially. Because of this growing population, it is necessary that health care providers outside university clinics also have knowledge about GD and its treatment, because HT can influence the course of several diseases^{32,33} and interact with several types of medication.³⁴ We also found that of all transgender people treated with HT, approximately 22% kept their gonads in situ. These people require special attention, because the long-term effects of HT on the testes, ovaries, and

uterus are not established. These topics and other possible complications, such as cancer risks, are subjects for further research.

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